PATENT
034827-2301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sun et al.
Title:	METHODS AND COMPOSITIONS FOR THE DETECTION OF MUCOLIPIDOSIS IV MUTATIONS
Appl. No.:	10/754,446
Filing Date:	January 9, 2004
Examiner:	Kapushoc, S.T.
Art Unit:	1634
Conf. No.:	7990

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

In response to the Examiner's Answer mailed September 7, 2007, Appellant submits this Reply Brief regarding the Final Rejection of claims 19-34. If any fee due is absent or incorrect, please charge or credit our Deposit Account No. 19-0741 for the appropriate amount.

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Status of Claims

Claims 1-18 and 35-36 have been cancelled.

Claims 19-34 are pending in the application.

Claims 19-34 are the subject of this appeal.

Grounds for Rejection to be Reviewed on Appeal

1. Claims 19 and 23-24 stand finally rejected under 35 U.S.C. § 103 as allegedly obvious over Edelmann et al. (Am. J. Hum. Genet. 70: 1023-1027, 2002), as evidenced by GenBank AF287270 (2000), in view of Doll et al. (Anal. Biochem. 301: 328-332, 2002).

2. Claims 25, 28, and 32-34 stand finally rejected under 35 U.S.C. § 103 as allegedly obvious over Edelmann et al. (Am. J. Hum. Genet. 70: 1023-1027, 2002), as evidenced by GenBank AF287270 (2000), in view of Doll et al. (Anal. Biochem. 301: 328-332, 2002).

3. Claims 20-22, 26-27, and 29-31 stand finally rejected under 35 U.S.C. § 103 as allegedly obvious over Edelmann et al. (Am. J. Hum. Genet. 70: 1023-1027, 2002) in view of Doll et al. (Anal. Biochem. 301: 328-332, 2002), GenBank AF287270 (2000), and Buck et al. (Biotechniques 27: 528-536, 1999).

Argument

Applicant respectfully reasserts the arguments set forth in the Appeal Brief filed May 11, 2007, and takes this opportunity to address the two deficiencies in the obviousness rejection asserted by the Examiner.

1. The cited prior art fails to teach a method for the real-time detection of a deletion mutation.

Relevant to the instant invention are two different MCOLN1 gene mutations that have been identified as being clinically significant. The first is a deletion mutation characterized by a 6.4 kb deletion that encompasses exons 1-7. The second is a polymorphism mutation (i.e. "point mutation") characterized by an A-to-G transition that results in a splicing defect. The point mutation is contained within the genomic region deleted in the deletion mutation. Thus, the two MCOLN1 mutations generate only three possible alleles: the wildtype, the A>G point mutation, and the deletion mutation.

Applicant's claimed invention relates to real-time PCR methods for detecting these mutations. Claims 19 and 25, the two independent claims that are the subject of this appeal, each encompass a real-type PCR method that includes detection of the deletion mutation. As discussed in more detail below, the prior art cited by the Examiner does not provide a real-type PCR-based method for detecting any deletion mutation, let alone the deletion mutation of the MCOLN1 gene.

Edelmann et al. disclose a multi-step method for detecting MCOLN1 gene mutations. Edelmann et al. first perform a multiplex PCR amplification that results in one amplicon from the deletion mutant, if present, and a second amplicon encompassing the site of the point mutation. The PCR product(s) are immobilized and probed with radio-labeled allele-specific oligonucleotides for the point mutation, its wildtype, and the deletion mutation.[1] Thus, the Edelmann method requires at least two temporally distinct steps: amplification and detection by

[1] Edelmann et al. at page 1024, right column, first paragraph.

standard probe hybridization. As acknowledged by the Examiner, Edelmann et al. fail to disclose a real-time PCR method for detecting mutations in the MCOLN1.[2]

Doll et al. does not remedy this deficiency. Doll et al. provide a method for detecting single nucleotide polymorphisms (i.e., point mutations) in the NAT1 gene using fluorogenically-labeled probes. But, Doll et al. do not teach or suggest a method for detecting deletion mutations, as required by claims 19 and 25. Doll et al. recognized the existence of deletion mutations in the NAT1 gene,[3] but despite this recognition, Doll et al. do not present a method for detection of the deletion. Thus, the prior art cited by the Examiner does not provide any real-time PCR-based method for detecting deletion mutations.

In rejecting claims 19 and 25, the Examiner has failed to identify in the prior art a real-time method for detecting deletion mutations. In order to remedy this deficiency, the Examiner reads far beyond the teachings of the cited prior art. In doing so, the Examiner relies purely and improperly on a hindsight analysis, using nothing more than Appellants' specification, to "adapt" the method of Doll et al. for the detection of a deletion mutation simply because it is feasible to do. Furthermore, with respect to claim 25, the Examiner has failed to identify in the prior art a real-time method for detecting both a deletion mutation and a point mutation in any gene. Thus, Applicant submits that the Examiner has failed to make a *prima facie* case of obviousness. This rejection should be reversed and withdrawn.

2. Applicant takes issue with the Examiner's claim construction.

The Examiner incorrectly construes the appealed claims. Although this mistake in claim construction does not alter the interpretation or application of the cited prior art, Applicant wishes to clarify the record with respect to the scope of the claims.

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[2] Examiner's Answer mailed September 7, 2007, at paragraph bridging pages 5 and 6.

[3] Doll et al. at Table 1.

The Examiner alleges that the primers and probes recited in claim 19 may contain as few as two nucleotides complementary to the MCOLN1 gene in each of the identified regions.[4] Specifically, the Examiner alleges that

> the first oligonucleotide primer minimally requires any sequence (which can be as little as two contiguous base pairs) that is complementary to any portion of a 15-30 bp segment (where the claim does not require a sequence complementary to the entire 15-30 bp segment; e.g. the sequence 5'-TT-3' is complementary to the 15 base DNA segment 5'-ACCGTATGCAAGCTC-3' because 5'-TT-3' is complementary to the positions 10-11 of the DNA segment within positions 100-500 of the MCOLN1 gene. Claim 19 further requires another primer and a probe, each with equal breadth.
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> Examiner's Answer mailed September 7, 2007, at p. 16, ll. 6-13 (emphasis added).

This interpretation is clearly flawed. Claim 19 requires that the first and second oligonucleotide primers comprises "a sequence complementary to a 15-30 bp segment of DNA." Likewise, the oligonucleotide probe recited in claim 19 must comprise "a sequence complementary to a 13-30 bp segment" of the MCOLN1 amplicon. The Examiner's interpretation that these oligonucleotides may contain as few as two nucleotide bases complementary to the identified sequences is simply not something encompassed by the claims.

When the claims are properly construed, one of skill in the art would recognize that the oligonucleotide primers must have at least 15 contiguous nucleotides that are complementary to the MCOLN1 gene in the specified region. Likewise, the oligonucleotide probe must have at least 13 contiguous complementary nucleotides.

Notwithstanding this misinterpretation of the breadth of the claimed invention, Applicant agrees with the Examiner's assertion that the MLIV-3UPS, MLIV-4UPS, and oligonucleotide probe of Edelmann et al. satisfy the respective limitations of claim 19, with the exception that the Edelmann probe does not contain a fluorophore or quencher moiety.

[4] Examiner's Answer mailed September 7, 2007, at p. 16.

Conclusion

For the reasons discussed above, Appellants respectfully submit that claims 19-34 are in condition for allowance, and respectfully request that the rejections be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,

Date: 11/07/2007

By: _____

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